UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/589,870	06/05/2000	Stephen C. Goshorn	690022.547	1301

500 7590 06/10/2005

SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 6300
SEATTLE, WA 98104-7092

EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/589,870	GOSHORN ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-22,24,26-32,37 and 67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-22,24,26-32,37 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 June 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20050329*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed March 22, 2005 is acknowledged and has been entered. Claims 25, 38-39, and 65 have been canceled. Claims 18, 24, and 27 have been amended. Claim 67 has been added.

2. Claims 18-22, 24, 26-32, 37, and 67 are pending in the application and are currently under prosecution.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The following Office action contains NEW GROUNDS of rejection necessitated by amendment.

Information Disclosure Statement

5. The information disclosure filed March 29, 2005 has been considered. An initialed copy is enclosed.

Grounds of Objection or Rejection Withdrawn

6. Unless specifically reiterated below, Applicant's amendment filed March 22, 2005 has obviated or rendered moot the grounds of objection or rejection set forth in the previous Office action mailed September 22, 2004.

Ground of Objection Maintained

Specification

7. The objection to the specification because the use of improperly demarcated trademarks is maintained. Although the use of trademarks is permissible in patent applications, the

proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Although Applicant has made a bona fide attempt to resolve this issue by appropriately amending the specification, additional examples of improperly demarcated trademarks have been noted, which include Varian™ Dynamax™ (page 36, line 19) and Varian™ Star™ (page 42, line 16).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 102

8. The rejection of claims 18-22, 24, 26, and 28-32 under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,571,894 A (of record), as evidenced by Database PIR 78 Accession No. A23513 (03 November 1987) (see USPTO search report "us-09-589-870b-2.rpr", result 1; Exhibit I), Kumar et al. (*Semin. Oncol.* **28**: 27-32, 2001), and US Patent No. 6,451,995 B1 (of record), is maintained.

At page 17 of the amendment filed March 22, 2005, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Claims 18-22 are drawn to a recombinant fusion protein comprising at least a first and a second polypeptide joined end to end, wherein the first polypeptide comprises amino acids 25 to 183 of streptavidin (SEQ ID NO: 2), wherein said second polypeptide is an antibody or antigen-binding fragment thereof that binds a neoangiogenic antigen and wherein said fusion protein is expressed as a soluble protein in the periplasmic space (claim 18), wherein said first and second polypeptides are separated by a linker of at least 2 or 4 amino acids (claims 19 and 20,

respectively), or wherein said linker consists of between 4 and 20 amino acids (claim 21) or between 5 and 10 amino acids (claim 22). Claims 24, 26, 28-32, 38, and 39 are drawn to the fusion protein of claim 18, wherein said fusion protein is capable of forming a tetrameric complex with a second, third, and fourth fusion protein (claim 24), or wherein said antibody is a single-chain Fv antibody fragment (claim 26), or wherein a linker connects the variable light and variable heavy chains of the single-chain antibody (claim 28), wherein the linker comprises at least 10, 15, or 20 amino acids (claims 29, 30, and 31, respectively), wherein the linker comprises at least four repeats of SEQ ID NO: 47 (claim 32).

US Patent No. 5,571,894 A ('894) teaches a fusion protein comprising streptavidin from *Streptomyces avidinii*, which is capable of strongly binding biotin, and a single-chain antibody (scFv) that binds Her2/neu (encoded by *c-erbB-2*); see the entire document (e.g., the abstract; and column 3, lines 12-29). '894 teaches the fusion protein is expressed as a soluble recombinant protein in the periplasm; see, e.g., column 32, lines 60-68; and column 33, lines 22-41. '894 teaches that streptavidin and the scFv is adjoined by a linker (i.e., peptide spacer) of one or more amino acids, e.g., 1-10 amino acids; see, e.g., column 6, lines 18-20. '894 teaches the heavy and light chain variable domains of the scFv is adjoined by a linker (i.e., peptide spacer) of about 10 to 30, e.g., around 15 amino acids; see, e.g., column 6, lines 1-17. '894 teaches the linker adjoining the heavy and light chain variable domains of the scFv consists of repeats of the sequence "GGGGS", which is identical to the sequence set forth as SEQ ID NO: 47 in the instant application; see, e.g., column 29, lines 48-55. Because '894 teaches such a linker consists of tandem repeats of the sequence "GGGGS" and that the linker is about 10 to 30 amino acids in length, '894 teaches that the linker adjoining the heavy and light chain variable domains of the scFv consists of up to six, or at least four repeats of SEQ ID NO: 47.

'894 teaches a fusion protein comprising streptavidin from *Streptomyces avidinii,* which is capable of strongly binding to biotin (column 3, lines 27-29), but does not teach the fusion protein is a "genomic streptavidin fusion protein" that comprises a first polypeptide comprising "amino acids 1 to 159 of full-length streptavidin, corresponding to amino acids 25 to 183 as set forth in SEQ ID NO:2" (claim 18). At page 6 (lines 12 and 13), the specification defines "genomic streptavidin", as used therein, as "a sequence comprising at least 129 residues of the sequence set forth in Figure 4 [i.e., SEQ ID NO: 2]". As evidenced by Database PIR 78

Accession No. A23513 (Exhibit I), streptavidin isolated from *Streptomyces avidinii* is a protein having an amino acid sequence of 183 amino acids that is identical to SEQ ID NO: 2. Accordingly, since the streptavidin molecule of the prior art is from *Streptomyces avidinii* and is capable of strongly binding biotin, the prior art appears to teach a fusion protein comprising a streptavidin molecule that is the same as "genomic streptavidin". Therefore, absent a showing of any difference, the fusion protein of '894 comprising streptavidin from *Streptomyces avidinii,* which is capable of strongly binding to biotin, is deemed the same as the "genomic streptavidin fusion protein" of instant claims comprising a first polypeptide comprising "amino acids 1 to 159 of full-length streptavidin, corresponding to amino acids 25 to 183 as set forth in SEQ ID NO:2", since the streptavidin molecule of the fusion protein of the prior art is identical to SEQ ID NO: 2. The Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed fusion protein. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed fusion protein is different than that taught by the prior art.

Kumar et al. teaches that c-erbB-2 encodes the human epidermal growth factor receptor 2 (HER2), which is overexpressed or amplified in several human malignancies; see the entire document (e.g., the abstract). Kumar et al. teaches overexpression of HER2 in human tumor cells is closely associated with increased angiogenesis; see, e.g., the abstract. Therefore, absent a showing of any difference, the fusion protein of the prior art is deemed the same as the claimed fusion protein, since, as evidenced by Kumar et al., the growth factor receptor HER-2, which is encoded by *c-erbB-2*, is a "neoangiogenic antigen" closely associated with angiogenesis in neoplastic cells and tissues, such as malignant tumors. In further support of this interpretation of the claims, it is noted that, at page 3, line 30, the specification discloses the fusion protein can comprise a single-chain antibody that binds "her2/neu".

US Patent No. 6,451,995 B1 teaches a fusion protein comprising a streptavidin and a single-chain antibody is capable of forming a tetrameric complex with a second, third, and fourth fusion protein, as recited in claim 24; see the entire document (e.g., column 64, lines 8-13). Therefore, absent a showing of any difference, the fusion protein of the prior art is deemed the same as the claimed fusion protein, since, as evidenced by US Patent No. 6,451,995 B1, the

fusion protein of the prior art is reasonably expected to be capable of forming a tetrameric complex with a second, third, and fourth fusion protein.

At page 17 of the amendment, Applicant has asserted that the prior art does not anticipate the claimed invention, but to the contrary, as explained above, the prior art does do so.

Claim Rejections - 35 USC § 103

9. The rejection of claims 18-22, 24, 26, and 28-30 under 35 U.S.C. 103(a) as being unpatentable over Alvarez-Diez et al. (*Nucl. Med. Biol.* **23**: 459-466, 1996) in view of Goshorn et al. (*Cancer Research* **53**: 2123-2127, 1993) (of record) and WO 89/03422 A, as evidenced by Guan et al. (*Appl. Microbiol. Biotechnol.* **44**: 753-758, 1996) (of record), is maintained.

At pages 17-19 of the amendment filed March 22, 2005, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Claims 18-22 are drawn to a recombinant fusion protein comprising at least a first and a second polypeptide joined end to end, wherein the first polypeptide comprises amino acids 25 to 183 of streptavidin (SEQ ID NO: 2), wherein said second polypeptide is an antibody or antigen-binding fragment thereof that binds TAG72, and wherein said fusion protein is expressed as a soluble protein in the periplasmic space (claims 18), wherein said first and second polypeptides are separated by a linker of at least 2 or 4 amino acids (claims 19 and 20, respectively), or wherein said linker consists of between 4 and 20 amino acids (claims 21) or between 5 and 10 amino acids (claim 22). Claims 24, 26, 28-30, 38, and 39 are drawn to the fusion protein of claim 18, wherein said fusion protein is capable of forming a tetrameric complex with a second, third, and fourth fusion protein (claim 24), or wherein said antibody is a single-chain Fv antibody fragment (claim 26), or wherein a linker connects the variable light and variable heavy chains of the single-chain antibody (claim 28), wherein the linker comprises at least 10 or 15 amino acids (claims 29 and 30, respectively).

At page 24, lines 20-22, the specification discloses: "Accordingly, in one embodiment of the present invention, scFvSA is a conjugate (fusion) of the targeting moiety (scFv) and ligand

(streptavidin)". While such an embodiment might be produced by chemically conjugating an scFv and streptavidin, claim 18, as amended by the paper filed June 17, 2004, recites, "wherein said fusion protein is expressed as a soluble protein in the periplasmic space"; therefore, the claims are presently drawn to a fusion protein produced by recombinant DNA technology in bacteria, as opposed to a fusion protein produced by chemically conjugating its component proteins.

Alvarez-Diez et al. teaches a fusion protein for pretargeted tumor imaging in nude mice bearing subcutaneuous LS174T human colon cancer xenografts (abstract). The fusion protein is comprised of streptavidin chemically conjugated to anti-TAG72 monoclonal antibody CC49; see entire document, e.g., the abstract and page 460, column 1.

Alvarez-Diez et al. does not expressly teach such a fusion protein, which is produced by recombinant DNA technology as a soluble protein in the periplasmic space, wherein streptavidin and the antibody are separated by a linker of between 5 and 10 amino acids; nor does Alvarez-Diez et al. expressly teach substituting a single-chain Fv antibody fragment derived from monoclonal antibody CC49, which single-chain Fv antibody fragment comprises a linker connecting the light and heavy chain variable chains by at least 15 amino acid residues.

Goshorn et al. teaches a recombinant DNA method for preparing a fusion protein comprising an antibody and an enzyme for two-step pretargeting tumors for imaging or treatment; see entire document (e.g., the introduction). Goshorn et al. teaches chemical conjugates can be highly heterogenous due to the lack of specificity inherent in the cross-linking reagents used (page 2123, column 2). Goshorn et al. suggests there may be significant advantages in using recombinant methods for the preparation of antibody-enzyme conjugates, since uniform products are obtained that should have more predictable biological properties (page 2123, column 2). Goshorn et al. teaches a genetic construction encoding a fusion protein comprising an antibody and an enzyme, wherein the antibody and the enzyme are adjoined by a linker of six amino acids; see, e.g., page 2124, Figure 1. Goshorn et al. discloses the recombinant fusion protein binds tumor cells at least as well as the chemically conjugated fusion protein (abstract). Goshorn et al. discloses another advantage of genetically engineering fusion proteins, namely that the fusion proteins can be produced using prokaryotic expression systems, which grow rapidly and inexpensively (page 2126, column 2). In addition, Goshorn et al.

teaches single-chain Fv fragments of antibodies with desired specificity afford the opportunity of maintaining the antigen-binding characteristics of the multichain parental antibody on a single molecule that is a fraction of the molecular weight (page 2126, paragraph bridging columns 1 and 2). Goshorn et al. teaches single-chain antibody fragments have been shown to offer advantages over whole antibody with respect to tumor penetration and clearance from circulation (page 2126, column 2). Goshorn et al. teaches a single-chain antibody comprising a heavy and light chain linked by an amino acid sequence of 18 residues (page 2123, column 2).

WO 89/03422 A (Edwards) teaches a synthetic DNA molecule encoding a streptavidin molecule, which comprises an amino acid sequence that is identical to the amino acid sequence set forth as SEQ ID NO: 2 in the instant application; see entire document (e.g., Figure 2). Edwards discloses the DNA molecule can be used to produce a genetic construct encoding a fusion protein possessing biotin binding activity, which comprises the amino acid sequence of the streptavidin fused to the amino acid sequence of any other protein; see, e.g., page 4, paragraph 4.

It would have been obvious to one ordinarily skilled in the art at the of the invention to produce a recombinant fusion protein for pretargeted tumor imaging or therapy comprising streptavidin and a scFv antibody having binding specificity for TAG72 by recombinant DNA technology, as opposed to chemical conjugation, using a DNA construct comprising the synthetic DNA molecule disclosed by WO 89/03422 A (Edwards) joined to a DNA molecule encoding the scFV, because Goshorn et al. teaches the necessary methodology and suggests that recombinant methodology offers advantages over chemical methodology, namely the production of more uniform products that should have more predictable biological properties and the capability of using prokaryotic expression systems, which grow rapidly and inexpensively. Furthermore, it would have been obvious to one ordinarily skilled in the art at the of the invention to produce a scFv fragment of monoclonal antibody CC49, instead of the whole monoclonal antibody used by Alvarez-Diez et al., to produce a fusion protein for pretargeted tumor imaging or therapy comprising streptavidin and a scFv antibody having binding specificity for TAG72, because Goshorn et al. suggests the use of the scFv, rather than the monoclonal antibody, offer advantages over whole antibody with respect to tumor penetration and clearance from

circulation. One ordinarily skilled in the art at the time of the invention would have been motivated to do so to study the potential of the fusion protein in imaging or treating tumors.

Guan et al. teaches that when the streptavidin gene from *S. avidinii* was expressed in *E. coli* as a non-fusion protein, the streptavidin protein accumulated primarily in inclusion bodies; but Guan et al. discloses that a fusion protein comprising streptavidin is expressed *as soluble protein* in *E. coli*; see the entire document (e.g., the abstract). Therefore, although neither Alvarez-Diez et al. nor Goshorn et al. suggest that a fusion protein comprising streptavidin and the single-chain antibody, which is produced by recombinant DNA technology in bacteria, is expressed as a soluble protein in the periplasm, absent a showing of any difference, said fusion protein is deemed the same as the fusion protein of claim 24. The Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed fusion protein, which is expressed as a soluble fusion protein in the periplasm. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed fusion protein is different than that taught or suggested by the prior art.

At page 18, Applicant has argued that given the prior art, the artisan of ordinary skill would have only been "tempted" to produce the claimed invention. Whether there is a legal distinction between "temptation" and "motivation" in terms of establishing the obviousness of the claimed invention in light of the prior art, cited as a basis for the rejection, seems unlikely. The Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, motivation or "temptation", if you will, to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one ordinarily skilled in the art at the of the invention would have been "tempted", yes, but moreover motivated to produce a recombinant fusion protein for pretargeted tumor imaging or therapy comprising streptavidin and a scFv antibody having binding specificity for TAG72 by recombinant DNA technology, as opposed to chemical conjugation, using a DNA construct comprising the synthetic DNA molecule disclosed

by WO 89/03422 A (Edwards) joined to a DNA molecule encoding the scFV, because Goshorn et al. teaches the necessary methodology and suggests that recombinant methodology offers advantages over chemical methodology, namely the production of more uniform products that should have more predictable biological properties and the capability of using prokaryotic expression systems, which grow rapidly and inexpensively. Furthermore, one ordinarily skilled in the art at the of the invention would have been motivated to produce a scFv fragment of monoclonal antibody CC49, instead of the whole monoclonal antibody used by Alvarez-Diez et al., to produce a fusion protein for pretargeted tumor imaging or therapy comprising streptavidin and a scFv antibody having binding specificity for TAG72, because Goshorn et al. suggests the use of the scFv, rather than the monoclonal antibody, offer advantages over whole antibody with respect to tumor penetration and clearance from circulation.

At page 18, Applicant has asserted that the use of recombinant DNA technology "resulted in surprisingly successful production of the recombinant fusion proteins", which are the claimed invention. In reply, Goshorn et al. teaches the methodology necessary to produce the claimed fusion proteins using recombinant DNA technology and specifically suggests that recombinant methodology offers advantages over chemical methodology. Given that the use of such technology to produce recombinant proteins was largely a matter of convention and routine at the time of the invention, it cannot be understood why Applicant was surprised to discover that the claimed fusion protein could be produced successfully. Why did Applicant not believe that such technology could be used to successfully produce the claimed invention, only to later be surprised by their success?

At page 19 of the amendment, Applicant has noted that the prior art (i.e., WO 89/03422 A) discloses it is by no means easy to predict the design of an improved streptavidin gene. In response, inasmuch as WO 89/03422 A provides just such a nucleic acid molecule encoding streptavidin for use in produce recombinant fusion proteins comprising streptavidin, there would be no need to predict the design of another.

Furthermore, at page 19, Applicant has asserted that the fusion protein of claim 24 "expresses at surprisingly high levels in the periplasm" and has argued that Guan et al. provides no evidence suggesting levels of expression in excess of those low levels commonly reported in the literature at the time. In response to Applicant's argument, which appears to be an assertion

that the reference fails to show certain features of Applicant's invention, it is noted that, while the claims are directed to a product, not a method for making the product, the features upon which Applicant relies (i.e., an expression level in the periplasm that exceeds some unspecified level) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, Guan et al. is cited as an evidentiary reference that absent a showing otherwise, the claimed fusion protein is expressed in the periplasm; as the claims are drawn to a fusion protein that is expressed as a soluble protein in the periplasm, it is of no consequence to what level the fusion protein is expressed, only that it is expressed in the periplasm as a soluble protein.

Finally, at page 19, Applicant has asserted, "only in hindsight can the surprising success of the present invention appear obvious". It is unclear whether the surprising success to which Applicant has referred is the surprising success of making the claimed invention, or the surprising success of using the claimed invention. As the claims are drawn to neither the method of making nor the method of using a product, but rather to the product itself, it is unclear whether this argument has any relevance.

Nevertheless, in response to Applicant's apparent assertion that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

10. The rejection of claims 31 and 32 under 35 U.S.C. 103(a) as being unpatentable over Alvarez-Diez et al. (*Nucl. Med. Biol.* **23**: 459-466, 1996) in view of Goshorn et al. (*Cancer Research* **53**: 2123-2127, 1993) (of record) and WO 89/03422 A, as evidenced by Guan et al. (*Appl. Microbiol. Biotechnol.* **44**: 753-758, 1996) (of record), as applied to claims 18-22, 24, 26, 28-30, 38, 39, and 65 above, in further view of Desplancq et al. (*Protein Engineering* **7**: 1027-1033, 1994) (of record), is maintained.

At pages 19 and 20 of the amendment filed March 22, 2005, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Claims 31 and 32 are drawn to a recombinant fusion protein comprising a first polypeptide comprising amino acids 25 to 183 of streptavidin (SEQ ID NO: 2) and a single chain Fv fragment of monoclonal antibody that binds TAG72 comprising a light and heavy variable chain connected by a linker comprising at least 20 amino acid residues (claim 31), or more particularly by a linker comprising at least 4 repeats of SEQ ID NO: 47 (claim 32).

Alvarez-Diez et al., Goshorn et al., and WO 89/03422 A (Edwards) teach that which is set forth in the above rejection of claims 18-22, 24, 26, and 28-30 under 35 U.S.C. 103(a).

Alvarez-Diez et al. does not expressly teach substituting a single-chain Fv antibody fragment comprising a linker of at least 20 amino acid residues connecting the light and heavy variable chains (claim 31) or comprising a linker of at least 4 repeats of SEQ ID NO: 47 (claim 32); and Goshorn et al. does not expressly teach or suggest a single-chain antibody having such a linker.

Similar to the teachings of Goshorn et al., Desplancq et al. teaches single-chain antibody fragments of an anti-TAG72 monoclonal antibody, but Desplancq et al. teaches such that are derived from an antibody designated B72.3, as opposed to CC49; see entire document (e.g., abstract). Desplancq et al. also teaches the Fv is the smallest antibody fragment that displays the monovalent antigen binding ability of the full-length parent antibody (page 1027, column 1). Desplancq et al. also teaches single-chain Fv antibody fragments are of interest for clinical applications because their pharmacokinetics and biodistribution may be superior to those of whole antibodies in some clinical situations, notably for diagnosis of tumors (page 1027, column 1). Desplancq et al. teaches that single-chain Fv antibodies "are of interest for clinical applications because their pharmacokinetics and biodistribution may be superior to those of whole antibodies in some clinical applications" (page 1027, column 1). In addition, Desplancq et al. teaches that the single-chain fragments of antibodies can be produced in which the variable light chain and the variable heavy chain of the single-chain fragment of antibody are adjoined by a linker comprising at least 20 amino acids, wherein said linker consists of at least four repeats of

SEQ ID NO: 47, such that the resultant single-chain fragment of antibody is more soluble compared to one having a relatively shorter linker; see, e.g., the abstract. Desplancq et al. teaches that problems with precipitation, which are encountered during the manufacture of recombinant antibodies, might be overcome by the use of a longer linker separating the variable heavy and light chains of the scFv antibody. Desplancq et al. teaches, "precipitation problems can be overcome by utilizing longer linkers", as their results showed that the tendency of the scFv variants to form dimers or higher molecular weight species decreases with increasing linker length (page 1033, column 1).

It would have been obvious to one ordinarily skilled in the art at the of the invention to produce a fusion protein for pretargeted tumor imaging or therapy comprising streptavidin and a single chain Fv fragment of monoclonal antibody that binds TAG72 comprising a light and heavy variable chain connected by a linker comprising at least 4 repeats of SEQ ID NO: 47, since Desplancq et al. teaches a scFv antibody having the same binding specificity as the monoclonal antibody of Alvarez-Diez et al. and having a longer linker separating the variable heavy and light chains of the antibody than the linker of the scFv antibody suggested by the teachings of Goshorn et al. is more soluble and can overcome problems with precipitation that might be encountered during its manufacture. One ordinarily skilled in the art at the time of the invention would have been motivated to do so to study the potential of the fusion protein in imaging or treating tumors.

At page 20, Applicant has asserted that the presently claimed invention would not have been obvious to one ordinarily skilled in the art at the time of the invention. To the contrary, for the reasons provided above, the claimed invention would have been obvious in view of the combination of the references cited as a basis for this ground of rejection.

11. The rejection of claims 18-21, 24, 26, 28-30, and 37 under 35 U.S.C. 103(a) as being unpatentable over Dubel et al. (*Journal of Immunological Methods* **178**: 201-209, 1995) (of record) in view of Gallizia et al. (*Protein Expression and Purification* **14**: 192-196, 1998) (of record), Ohno et al. (*DNA and Cell Biology* **15**: 401-406, 1996) (of record), and McLaughlin et al. (*Oncology* **12**: 1763-1769, 1998) (of record), as evidenced by Kipriyanov et al. (*Human Antibodies and Hybridomas* **6**: 93-101, 1995) (of record) and Database PIR 78 Accession No.

A23513 (03 November 1987) (see USPTO search report "us-09-589-870b-2.rpr", result 1; Exhibit I), is maintained.

At pages 20 and 21 of the amendment filed March 22, 2005, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Claims 18-21, 27, and 37 are drawn to a recombinant fusion protein comprising at least a first and a second polypeptide joined end to end, wherein the first polypeptide comprises amino acids 25 to 182 of streptavidin (SEQ ID NO: 2), wherein said second polypeptide is an antibody or antigen-binding fragment thereof binds CD20, and wherein said fusion protein is expressed as a soluble protein in the periplasmic space (claims 18 and 37), wherein said first and second polypeptides are separated by a linker of at least 2 or 4 amino acids (claims 19 and 20, respectively) or consists of between 4 and 20 amino acids (claims 21). Claims 24, 26, and 28-30 are drawn to the fusion protein of claim 18, wherein said fusion protein is capable of forming a tetrameric complex with a second, third, and fourth fusion protein (claim 24), or wherein said antibody is a single-chain Fv antibody fragment (claim 26) comprising a linker connecting the variable light and variable heavy chains (claim 28), wherein the linker comprises at least 10 or 15 amino acids (claims 29 and 30, respectively). Claim 27 is drawn to the fusion protein of claim 26, which comprises a single-chain Fv fragment of an antibody that binds CD20 and "is derived from the variable light and variable heavy domains of antibody B9E9, SEQ ID NO:8"

Dubel et al. teaches a fusion protein, and a composition thereof, comprising at least a first and a second polypeptide joined end to end, wherein the first polypeptide comprises a portion of genomic streptavidin and wherein said second polypeptide is an antibody or antigen-binding fragment thereof, wherein said first and second polypeptides are separated by a linker consisting of 5 amino acids; see the entire document. Dubel et al. teaches the fusion protein is capable of forming a tetrameric complex with a second, third, and fourth fusion protein. The fusion protein of Dubel et al. comprises a single-chain Fv antibody fragment in which a linker connects the variable light and variable heavy chains. As evidenced by Kipriyanov et al., the linker connecting the variable light and variable heavy chains consists of 15 amino acids. In addition, Dubel et al. teaches that single-chain Fv antibodies (scFv) "represent potentially very useful

molecules for the targeted delivery of drugs, toxins, or radionuclides to a tumour site" (page 201, column 2). Dubel et al. discloses, "various heterologous protein moieties can also be genetically fused to scFv antibodies to generate bifunctional fusion proteins" (page 202, column 1). Additionally, Dubel et al. teaches that streptavidin "exhibits one of the strongest noncovalent binding affinities known for a biomolecule", namely biotin (page 208, column 1). Dubel et al. teaches that the fusion protein comprising a single-chain antibody and streptavidin might be "usefully employed for the in vitro purging of autologous bone marrow transplants to eliminate B lymphocytes in the treatment of leukemias and malignant lymphomas" (page 208, column 1).

The single-chain antibody of the fusion protein of Dubel et al. is derived from a monoclonal antibody that binds the "215" epitope of *D. melanogaster* RNA polymerase II; however, Dubel et al. does not teach a fusion protein comprising an antibody or single-chain fragment of an antibody that binds specifically to CD20, which "is derived from the variable light and variable heavy domains of antibody B9E9, SEQ ID NO:8".

The first polypeptide of the fusion protein of Dubel et al. consists of 126 amino acids of streptavidin; however, Dubel et al. does not expressly teach that the first polypeptide of the fusion protein can comprise at least 129 amino acids of streptavidin, as set forth in SEQ ID NO: 2.

McLaughlin et al. teaches that CD20 is an appealing target for a therapeutic antibody, because it is expressed on B cells, and progenitors thereof, from the pre-B cell stage to the activated B cell stage, but not on stem cells, normal plasma cells, or cells of other lineages; see the entire document (e.g., page 1763, columns 2 and 3). McLaughlin et al. discloses that CD20 is expressed on most B cell lymphomas and chronic lymphocytic leukemias and on 50% of pre-B cell acute lymphoblastic leukemias (page 1763, column 3). McLaughlin et al. teaches the clinical status and optimal use of Rituximab™, a recombinant humanized monoclonal antibody that specifically binds CD20 (abstract). Mclaughlin et al. discloses, "as the first MoAb [monoclonal antibody] to gain FDA approval for the treatment of a malignancy, rituximab signals the beginning of a promising new era in cancer therapy" (abstract). McLaughlin et al. teaches the chimeric antibody inhibits the growth of cancer cells expressing CD20 by a mechanism involving complement-dependent cytotoxicity. McLaughlin et al. also discloses that

the antibody sensitizes cancer cells to the cytotoxic effects of drugs and toxins; see, e.g., page 1764, column 3.

Ohno et al. teaches that tissue-specific delivery of a variety of molecules is a valuable technique for medical research; see the entire document, e.g., the abstract. Ohno et al. discloses, "the cell-targeting moiety can be either antibodies or protein ligands (growth factors) that recognize the corresponding antigens or receptor (page 401, column 1). Ohno et al. demonstrates a streptavidin-ligand fusion protein, ST-TGF-α, can efficiently target biotinylated protein to cells that express the ligand's receptor (abstract). Ohno et al. teaches that streptavidin-ligand and streptavidin-antibody fusion proteins have a number or advantages over immunotoxins and recombinant toxins for treatment of disease, namely cancer; see, e.g., page 401, columns 1 and 2; and page 404, columns 1 and 2). Ohno et al. discloses: "Because biotin can be easily incorporated into a wide range of macromolecules without interfering with biological activities (Wilchek and Bayer, 1990) steptavidin containing-proteins such as ST-TGF-α have wider applicability as bridges to deliver specific molecules such as toxins" (page 405, column 1). Then, Ohno et al. teaches, "other chimeric molecules in which the TGF-α moiety has been replaced by an alternate targeting element may have equally broad applicability to targeting a variety of cell types with equal affinities" (page 405, column 2).

Gallizia et al. teaches a fusion protein comprising residues 15 to 159 of streptavidin, which is expressed in *E. coli* as a soluble protein; see the entire document (e.g., the abstract; and page 196, column 1). Gallizia et al. discloses that streptavidin is generally expressed in *E. coli* as an insoluble protein (abstract); therefore, Gallizia et al. teaches that a recombinant streptavidin molecule in which the first N-terminal residues are substituted with the T7-tag peptide can be used advantageously, because it can be produced in *E. coli* as a soluble and functional protein, which can be purified in two simple steps with yields of 70 mg per liter of culture; see, e.g., the abstract. Gallizia et al. teaches the recombinant fusion protein and natural streptavidin bind biotin with very similar affinity; see, e.g., page 196, column 1. Gallizia et al. teaches the biotin binding characteristics of the recombinant fusion protein are consistent with that which would be expected for a tetravalent structure, which suggests that a molecule of the fusion protein is

capable of forming a tetrameric complex with a second, third, and fourth molecule of the fusion protein (page 195, column 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the fusion protein of Dubel et al. to produce a fusion protein comprising a first polypeptide and a second polypeptide, wherein the first polypeptide is single-chain Fv antibody that binds CD20. One of ordinary skill in the art would have appreciated the fact that, based upon the teachings of Dubel et al., McLaughlin et al., and Ohno et al., the fusion of such an antigen-binding fragment and streptavidin could be used simultaneously to inhibit the growth of cancer cells expressing CD20 by a mechanism involving complement-dependent cytotoxicity and to selectively and specifically target biotin-conjugated drugs, toxins, or radionuclides to a CD20+ lymphoma tumor cell, because McLaughlin et al. teaches that anti-CD20 antibody-directed therapy can be used effectively to treat patients diagnosed with lymphoma, because Dubel et al. and Ohno et al. teach or suggest the utility of targeting drugs, toxins, or radionuclides to cancer cells using single-chain antibody fusion proteins comprising streptavidin, and finally because McLaughlin et al. teaches that an anti-CD20 antibody can sensitize cancer cells to the cytotoxic effects of drugs and toxins. One of ordinary skill in the art would have been motivated have modified the fusion protein of Dubel et al. in this manner to treat lymphoma, for example.

Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have replaced core streptavidin of the fusion protein of Dubel et al. with the recombinant streptavidin molecule of Gallizia et al., because Gallizia et al. discloses a recombinant streptavidin molecule in which the first N-terminal residues are substituted with the T7-tag peptide can be used advantageously, since it can be produced in *E. coli* as a soluble and functional protein. One of ordinary skill in the art at the time the invention was made would have been motivated to make the replacement because the teachings of Gallizia et al. suggest that the making the replacement would be advantageous.

Gallizia et al. teaches a cDNA molecule encoding amino acids 15-159 of "mature streptavidin" from *Streptomyces avidinii,* which is capable of strongly binding to biotin (see, e.g., page 193, column 2, and page 195, Figure 3); however, Gallizia et al. does not disclose the amino acid sequence of the streptavidin molecule. As evidenced by Database PIR 78 Accession

No. A23513 (Exhibit I), streptavidin isolated from *Streptomyces avidinii* is a protein having an amino acid sequence of 183 amino acids that is identical to SEQ ID NO: 2. Since the streptavidin molecule of the prior art is from *Streptomyces avidinii,* comprises amino acids 15 to 159 of "mature streptavidin", and is capable of strongly binding biotin, the prior art appears to teach a streptavidin molecule that is the same as "genomic streptavidin", which at page 6 the specification defines as a polypeptide comprising at least 129 amino acids of streptavidin, as set forth in SEQ ID NO: 2. Therefore, absent a showing of any difference, the fusion protein of the prior art, which comprises a streptavidin molecule according to Gallizia et al., is deemed the same as the "genomic streptavidin fusion protein" of instant claims. The Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed fusion protein. For example, the Office does not have the facilities to produce the streptavidin encoded by the cDNA molecule of Gallizia et al. to determine if the molecule comprises at least 129 amino acids of the amino acid sequence set forth as SEQ ID NO: 2 and is, otherwise, distinct from the claimed "genomic streptavidin fusion protein". In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed fusion protein is different than that taught by the prior art.

With further regard to claim 27, the prior art cited as the basis for this ground of rejection does not teach or suggest that the fusion protein comprising a single-chain antibody Fv fragment that binds CD20 and "is derived from the variable light and variable heavy domains of antibody B9E9, SEQ ID NO:8". Nevertheless, because the method by which the single-chain Fv fragment of the fusion protein, which binds CD20, is derived is not described, it cannot be determined how such a derivation process would alter the structure or function of the fusion protein that would have been obvious at the time the invention was made in view of the cited references, which is otherwise identical to the claimed fusion protein (i.e., all other limitations of the claims are met). If, for example, the fusion protein were to be derived from the amino acids of which the variable light and variable heavy domains of antibody B9E9 or the polypeptide of SEQ ID NO: 8 are composed, it is submitted that there would be no structural or functional feature of either the fusion protein or the claimed fusion protein, which would permit one to distinguish one from the other. The naturally occurring amino acids derived from one protein cannot be distinguished

from those amino acids derived from any other protein, or any other source in general. As such, the unspecified process by which the claimed fusion protein is made (i.e., by a process that includes its derivation, at least in part, from "the variable light and variable heavy domains of antibody B9E9, SEQ ID NO:8") does not serve to distinguish the fusion protein that would have been obvious in light of the prior art from that which is now claimed. Consequently, given the broadest reasonable interpretation, the claims are not necessarily limited to fusion proteins that may only be produced using monoclonal antibody B9E9 or the polypeptide of SEQ ID NO: 8; in fact, as claimed, neither monoclonal antibody B9E9 nor the polypeptide of SEQ ID NO: 8 would necessarily have to be in one's possession before the claimed invention could be made. Notably, the Office does not have the facilities for examining and comparing Applicant's product produced by derivation from "the variable light and variable heavy domains of antibody B9E9, SEQ ID NO:8" with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed fusion protein. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed fusion proteins are different than those taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

At pages 20 and 21, Applicant has asserted that the presently claimed invention would not have been obvious to one ordinarily skilled in the art at the time of the invention. To the contrary, for the reasons provided above, the claimed invention would have been obvious in view of the combination of the references cited as a basis for this ground of rejection.

12. The rejection of claim 22 under 35 U.S.C. 103(a) as being unpatentable Dubel et al. (*Journal of Immunological Methods* **178**: 201-209, 1995) (of record) in view of Gallizia et al. (*Protein Expression and Purification* **14**: 192-196, 1998) (of record), Ohno et al. (*DNA and Cell Biology* **15**: 401-406, 1996) (of record), and McLaughlin et al. (*Oncology* **12**: 1763-1769, 1998) (of record), as evidenced by Kipriyanov et al. (*Human Antibodies and Hybridomas* **6**: 93-101, 1995) (of record) and Database PIR 78 Accession No. A23513 (03 November 1987) (see USPTO search report "us-09-589-870b-2.rpr", result 1; Exhibit I), as applied to claims 18-21, 24,

26, 28-30, 37, and 65 above, and in further view of Goshorn et al. (*Cancer Research* **53**: 2123-2127, 1993) (of record), is maintained.

At page 21 of the amendment filed March 22, 2005, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Claim 22 is drawn to the fusion protein of claim 21, wherein said linker is between 5 and ten amino acids (i.e., 6-9 amino acids).

Dubel et al., Gallizia et al., Ohno et al., and McLaughlin et al. teach that which is set forth above.

The first and second polypeptides of the fusion protein of Dubel et al. are adjoined by a linker, which consists of 5 amino acids, and the first and second polypeptides of the fusion protein of Gallizia et al. are not separated by a linker.

However, none of Dubel et al., Gallizia et al., Ohno et al., and McLaughlin et al. expressly teach that a fusion protein can comprise a first and second polypeptide adjoined by a linker of between 5 and 10 amino acids.

Goshorn et al. teaches that which is set forth above; in particular, Goshorn et al. teaches a fusion protein comprising a first and second polypeptide, which are joined by a linker of 6 amino acids.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Dubel et al. to produce and use a fusion protein comprising a first polypeptide and a second polypeptide, wherein the first and second polypeptides are separated by a linker that is 6 amino acids, because Goshorn et al. teaches a fusion protein comprising a first and a second polypeptide adjoined by a linker of 6 amino acids, which retains the ability to bind specifically to the antigen to which the antibody from the which the fusion protein is derived binds and retains the ability to bind specifically to the substrate to which the second polypeptide from which the fusion protein is derived binds. One of ordinary skill in the art at the time the invention was made would have recognized the equivalency of a linker consisting of 5 amino acids and a linker consisting of 6 amino acids, because the prior art teaches

that either a linker consisting of 5 amino acids or a linker consisting of 6 amino acids is suitable for use in the fusion protein. See MPEP §§ 2144.06 and 2144.07.

At page 21, Applicant has asserted that the presently claimed invention would not have been obvious to one ordinarily skilled in the art at the time of the invention. To the contrary, for the reasons provided above, the claimed invention would have been obvious in view of the combination of the references cited as a basis for this ground of rejection.

13. The rejection of claims 31 and 32 under 35 U.S.C. 103(a) as being unpatentable Dubel et al. (*Journal of Immunological Methods* **178**: 201-209, 1995) (of record) in view of Gallizia et al. (*Protein Expression and Purification* **14**: 192-196, 1998) (of record), Ohno et al. (*DNA and Cell Biology* **15**: 401-406, 1996) (of record), and McLaughlin et al. (*Oncology* **12**: 1763-1769, 1998) (of record), as evidenced by Kipriyanov et al. (*Human Antibodies and Hybridomas* **6**: 93-101, 1995) (of record) and Database PIR 78 Accession No. A23513 (03 November 1987) (see USPTO search report "us-09-589-870b-2.rpr", result 1; Exhibit I), as applied to claims 18-21, 24, 26, 28-30, 37, and 65 above, and in further view of Desplancq et al. (*Protein Engineering* **7**: 1027-1033, 1994) (of record), is maintained.

At pages 21 and 22 of the amendment filed March 22, 2005, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Claims 31 and 32 are drawn to a fusion protein comprising a first polypeptide comprising amino acids 25 to 182 of streptavidin (SEQ ID NO: 2) and a single chain Fv fragment of monoclonal antibody that binds TAG72 comprising a light and heavy variable chain connected by a linker comprising at least 20 amino acid residues (claim 31), or more particularly by a linker comprising at least 4 repeats of SEQ ID NO: 47 (claim 32).

Dubel et al., Gallizia et al., Ohno et al., and McLaughlin et al. teach that which is set forth in the rejection above.

The linker adjoining the variable light chain and the variable heavy chain of the single-chain antibody of the fusion protein of Dubel et al. consists of 15 amino acids.

However, none of Dubel et al., Gallizia et al., Ohno et al., and McLaughlin et al. expressly teach that the fusion protein can comprise an antibody or antigen-binding fragment thereof, wherein said antibody is a single-chain Fv fragment comprising a variable light chain and the variable heavy chain of the single-chain antibody, which are adjoined by a linker comprising at least 20 amino acids, wherein said linker is at least four repeats of SEQ ID NO: 47.

Desplancq et al. teaches that which is set forth above.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the fusion protein of Dubel et al. to produce a fusion protein comprising a first polypeptide and a second polypeptide, wherein the first polypeptide is single-chain Fv antibody comprising a variable light chain and a variable heavy chain of the single-chain antibody, which are adjoined by a linker comprising at least 20 amino acids, wherein said linker is at least four repeats of SEQ ID NO: 47, because Desplancq et al. teaches that single-chain antibodies can be produced in which the variable light chain and the variable heavy chain of the single-chain antibody is adjoined by a linker comprising at least 20 amino acids, wherein said linker is at least four repeats of SEQ ID NO: 47, such that the resultant antibody is more soluble compared to an antibody having a relatively shorter linker. One of ordinary skill in the art would have been motivated at the time the invention was made to separate the variable heavy and light chains of the single-chain Fv antibody by a linker consisting of at least four gly-gly-gly-gly-ser (SEQ ID NO: 47) linkers, because Desplancq et al. teaches that problems with precipitation, which are encountered during the manufacture of recombinant antibodies, might be overcome by the use of a longer linker separating the variable heavy and light chains of the scFv antibody.

Double Patenting

14. The provisional rejection of claims 18-22, 24, 26, 28-32, and 37 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18-24, 26, 27, 29-38, 40-42, and 79-81 of co-pending Application No. 10/013,173 is maintained.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

At page 10 of the amendment filed June 17, 2004 and again at page 22 of the amendment filed March 22, 2005, Applicant has requested that this issue be held in abeyance until allowable subject matter is identified.

New Grounds of Rejection

15. Claim 67 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "new matter" or "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

Claim 67 is drawn to a recombinant fusion protein comprising amino acids 3 to 423 of SEQ ID NO: 8. SEQ ID NO: 8 is the amino acid sequence depicted in Figure 11C, which is the amino acid sequence of a fusion protein comprising the amino acid sequences of a variable light chain region and variable heavy chain region of murine monoclonal antibody B9E9, which are adjoined by a linker, and further comprising the amino acid sequence of streptavidin, which is adjoined to the amino acid sequences of the variable light chain and variable heavy chain regions by a second linker.

While Applicant has not stated specifically wherein the specification support may be found, there is an assertion that the claim language is supported the specification, including the claims, as originally filed. To the contrary, however, the specification, including the claims, as originally filed, does not appear to provide sufficient written support for a recombinant fusion protein comprising amino acids 3 to 423 of SEQ ID NO: 8. It is noted that in Figure 11C there is a line drawn between the amino acids in positions 2 and 3 of the amino acid sequence depicted therein; however, this significance of this line is not annotated, either in the figure, its brief

description, or elsewhere in the specification. Other lines drawn between amino acids in the figure are annotated as the boundaries that separate the amino acid sequence of one element of the fusion protein from another, but the significance of the line drawn between the amino acids in positions 2 and 3 of the amino acid sequence cannot be surmised.

Due to the evident lack of written support for the claim language, the addition of claim 67 appears to introduce new matter, thereby violating the written description requirement. Nevertheless, even if it is assumed *arguendo* that the line drawn between the amino acids in positions 2 and 3 of the amino acid sequence were sufficient to support the claim language, it is submitted that because the significance of the line drawn between the amino acids in positions 2 and 3 of the amino acid sequence cannot be surmised, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

These issues might be resolved if Applicant were to point to specific disclosures in the specification, including the claims, as originally filed, that are believed to provide the necessary written support for the claim language and adequately describe the claimed invention, so as to reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

16. Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 is drawn to the fusion protein of claim 26, wherein the single-chain Fv fragment specifically binds CD20 and "is derived from the variable light and variable heavy domains of antibody B9E9, SEQ ID NO:8". The claim is indefinite because, as explained above, SEQ ID NO: 8 is not the amino acid sequence of the variable light and variable heavy domains of antibody B9E9, but rather the amino acid sequence depicted in Figure 11C, which is the amino acid sequence of a fusion protein comprising the amino acid sequences of a variable light chain region and variable heavy chain region of murine monoclonal antibody B9E9, which are adjoined by a linker, and further comprising the amino acid sequence of streptavidin, which is adjoined to the amino acid sequences of the variable light chain and variable heavy chain regions

by a second linker. Although the subject matter that Applicant regards as the invention is a fusion protein comprising a single-chain Fv antibody fragment that binds to CD20, it cannot be determined whether the single-chain Fv antibody of which the fusion protein is comprised is necessarily derived from the protein of SEQ ID NO; 8 or alternatively the variable light and variable heavy domains of antibody B9E9. If the latter, the Office would necessarily reinstate the ground of rejection previously set forth in section 9 of the preceding Office action mailed September 22, 2004.

Conclusion

17. No claim is allowed.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
June 8, 2005

LARRY R. HELMS, PH.D
PRIMARY EXAMINER